

REMARKS

Claims 89-117 are pending. Claims 89-110 and 114 are under examination.

Rejection Under 35 U.S.C. § 103(a)

Applicants respectfully traverse the rejection of claims 89-110 and 114 as allegedly rendered obvious under 35 U.S.C. § 103(a) by Froesch et al., *Proc. Am. Assoc. Cancer Res.* 89:13 (1998), in view of Takayama et al., *Cancer Res.* 58:3116-3131 (1998), Noordzij et al., *J. Urology* 158:1880-1885 (1997) and Sano et al., U.S. Patent No. 5,665,539. For the reasons of record and further as set forth below, Applicants maintain that claims 89-110 and 114 are unobvious over the cited references whether viewed individually or in combination.

To establish a *prima facie* case of obviousness, three basic criteria must be met, including that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings, and that a reasonable expectation of success must exist. Further, each of these three requirements must “be found in the prior art, and not to be based on applicant’s disclosure.” See MPEP §2143.

The Federal circuit has reaffirmed the Office’s high burden to establish a *prima facie* case of obviousness and has emphasized the requirement of specificity. See *In re Sang-Su Lee*, 277 F.3d 1338, 61 USPQ 2d 1430 (Fed. Cir. 2002). In *Lee*, the Federal Circuit held that “[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record.” *Id.* 277 F.3d at 1433 (emphasis added). Further, when considering differences between prior art and the claimed invention, “a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” MPEP §2141.02(VI).

Applicants believe that the Office has failed to provide any objective evidence when maintaining that the teaching of Froesch et al. in view of Takayama et al., Noordzij et al. and Sano et al. “would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the level of BAG-1 expressed in prostate cancer using immuno-PCR, compare the level with a reference level and further correlate the results with the

risk of tumor recurrence, tumor spread and survival in a patient suffering from prostate cancer.”

On pages 3-4 of the Office Action, the Office asserts that

Froesch et al. teach that BAG-1 protein (cytosolic BAG protein) is expressed in all 9/9 prostate cancer cell lines and 51/51 archival prostate tumor specimens (see abstract and title). [a] Takayama et al. teach that overexpression of BAG-1 has been shown to increase the metastatic potential of tumor cells in vivo (see page 3116, right column, 2nd paragraph, lines 5-7). [b] Takayama et al. teach that BAG-1 can promote cell survival and augment the bioactivities of several proteins known to be important for tumorigenesis (e.g. bcl-2, Raf-1, HGF-R, and PDGF-R) (see page 3117, left column, 3rd paragraph). [c] Takayama et al. teach that BAG-1 can be regarded as a candidate proto-oncogene (see page 3117, left column, 3rd paragraph). [d] Takayama et al. teach that BAG-1 protein is consistently the most abundant form of BAG-1 expressed in tumors (see page 3127, left column, 1st paragraph). [underlined and numbered for emphasis]

The Office concludes:

Therefore, in view of the teachings of Froesch and Takayama, one of ordinary skill of art would reasonable [*sic*] conclude that the presence of BAG-1 protein is correlated with the metastatic potential of tumor cells and BAG-1 will promote the cancer cell survival.

Applicants respectfully disagree and believe that the Office has relied on subjective evidence to establish a *prima facie* case of obviousness. Applicants disagree with Office’s conclusion that the teaching of Froesch et al., when combined with Takayama et al., Noordzij et al. and/or Sano et al., would render the claims obvious to a person of ordinary skill in the art:

First, a person of ordinary skill in the art who knew about the teaching of Froesch et al. and was familiar with the disclosure of Noordzij et al. and Sano et al., after reading the Takayama et al. reference, would have realized that the alleged teaching of Takayama et al. (a) *supra*, as broadly as stated, is not a conclusion based on the results disclosed in Takayama et al. but rather is a subjective interpretation of the source reference upon which it depends. On page 3116, right column, 2nd paragraph, lines 5-7, of the Takayama et al. reference, the quotation “BAG-1 has been shown to increase the metastatic potential of tumor cells *in vivo*” ends with footnote No. 4, which suggests that the quotation was based on an article by Yawata et al. (now a published paper, *Oncogene* 16:2681-2686 (1998), attached herewith as Exhibit 1) titled “Prolonged cell survival enhances peritoneal dissemination of gastric cancer cells.” Yawata et

al. reports that overexpression of Bcl-2 or BAG-1 enhances peritoneal dissemination of human gastric MKN74 cells in nude mice (see Yawata at page 2682, left column, paragraph 1, lines 3-5; and page 2684 under the heading of *peritoneal dissemination of MKN74 transfectants*). In other words, the Takayama et al. alleged teaching (a) should not have been interpreted broader than its source, the Yawata et al. reference, which was available to a person of ordinary skill in the art at the time the present invention was made. For a person having ordinary skill in the art and having the capability of appreciating the complexity of scientific issues in cancer, the BAG-1 effects in dissemination of gastric cancer cells in mice could have hardly provided any reasonable expectation of success for that person to want to apply the same concept to prostate cancer in human and coming up with a method of determining the risk of tumor recurrence or spread in patients suffering from prostate cancer, as claimed. Therefore, in contrast to the Office's contention, the teaching of Takayama et al., even in combination with Noordzij et al. and/or Sano et al. would not have cured the deficiencies of Froesch et al. or rendered the claimed invention obvious.

Second, a person of ordinary skill in the art who knew about the teachings of et al. and was familiar with the work of Noordzij et al. and Sano et al., after reading the Takayama et al. reference would have also realized that the alleged teachings of Takayama et al. (a, b, and c, *supra*) could not be relied on because, at the time the claimed invention was made, alternative reports in the cancer field taught that BAG-1 expression actually promoted host survival, not cell survival of cancer cells, in patients with early-stage breast cancer or nonsmall cell lung cancer (NSCLC). For example, in Turner et al. (*J. Clinical Oncology* 19(4):992-1000 (2001); attached as Exhibit 2), Figure 3 showed that high BAG-1 protein level was associated with improved overall survival (OS) and improved distant metastasis-free survival (DMFS) in patients with early-stage breast cancer. Also, Rorke et al. (*Int. J. Cancer (Pred. Oncol.)* 95:317-322 (2001), attached as Exhibit 3) correlated BAG-1 expression with overall survival in patients with NSCLC (see the abstract and figures, *Id*). Therefore, in view of such contrary reports, a person having ordinary skill in the art, at the time the invention was made, could not have been certain about any correlation of BAG-1 expression with host survival, let alone have a reasonable expectation of success of achieving the claimed methods.

Moreover, Noordzij et al. cannot cure the deficiencies of Froesch et al., alone or in combination with Takayama et al. and/or Sano et al., which is alleged to teach detection of a protein using immuno-PCR. The Office Action has previously asserted that Noordzij et al. describes determining the level of oncoprotein Bcl-2 and androgen receptor expression in pretreatment transurethral resection specimens of hormonally treated prostate cancer patients and correlating the results with tumor stage and grade and with the occurrence of clinical progression or tumor related death. However, Noordzij et al. found no correlation with Bcl-2. “The bcl-2 scores did not correlate with tumor stage or grade” (abstract). Noordzij et al. further indicates that “[A]ndrogen receptor scores were marginally related to tumor grade, but not to tumor stage” (abstract). Noordzij et al. states that a “prognostic value of bcl-2 or androgen receptor in pretreatment transurethral resection specimens was not found” (see abstract and page 1883, right column, first complete paragraph). Noordzij et al. found only a combined bcl-2/androgen receptor score to be an independent prognostic marker to predict clinical progression (see abstract and page 1883, right column, third paragraph).

In conclusion, a person of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success to combine the teachings of Froesch et al. with those of Takayama et al., Noordzij et al. and/or Sano et al. to arrive at the claimed methods. Therefore, Applicants respectfully maintain that the claimed methods are unobvious over Froesch et al., alone or in combination with Takayama et al., Noordzij et al. and/or Sano et al. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 89-110 and 114 as allegedly rendered obvious under 35 U.S.C. § 103(a).

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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A handwritten signature in cursive script, reading "Deborah L. Cadena".

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